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ORIGINAL REPORT

Group-Wide, Prospective Study of Ototoxicity Assessment in Children Receiving Cisplatin Chemotherapy (ACCL05C1): A Report From the Children's Oncology Group

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ABSTRACT

Purpose

Optimal assessment methods and criteria for reporting hearing outcomes in children who receive treatment with cisplatin are uncertain. The objectives of our study were to compare different ototoxicity classification systems, to evaluate the feasibility of including otoacoustic emissions and extended high frequency audiometry, and to evaluate a central review mechanism for audiologic results for cisplatin-treated children in the cooperative group setting.

Patients and Methods

Eligible participants were 1 to 30 years, with planned cisplatin-containing treatment. Hearing evaluations were conducted at baseline, before each cisplatin cycle, and at the end of therapy. Audiologic results were assessed and graded by the testing audiologist and by two central review audiologists using the American Speech-Language-Hearing Association Ototoxicity Criteria (ASHA), Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE), and Brock Ototoxicity Grades (Brock). One central reviewer also used the International Society of Pediatric Oncology Ototoxicity Scale (SIOP).

Results

At the end of treatment, the prevalence of any degree of ototoxicity ranged from 40% to 56%, and severe ototoxicity ranged from 7% to 22%. Compared with CTCAE, SIOP detected significantly more ototoxicity ($P = .004$), whereas Brock criteria detected significantly fewer patients with any or severe ototoxicity ($P < .001$ for both). SIOP detected ototoxicity earlier than did the other scales. Agreement between the central reviewers and the institutional audiologist was almost perfect for ASHA and Brock, whereas the poorest agreement occurred with CTCAE.

Conclusion

The SIOP scale may be superior to ASHA, Brock, and CTCAE scales for classifying ototoxicity in pediatric patients who were treated with cisplatin. Future studies should evaluate inter-rater reliability of the SIOP scale.

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INTRODUCTION

Cisplatin is a well-established chemotherapeutic agent that is used for several forms of childhood cancer, but its dose-limiting toxicity is hearing loss. Irreversible hearing loss occurs in approximately two thirds of children who are treated with cisplatin[1] and is almost universal in specific subsets, such as young children with neuroblastoma who are treated with cisplatin and carboplatin.[1-3] In children, cisplatin-induced ototoxicity has the potential to impact speech-language and social development, educatioxnal achievement, cognition, and quality of life.[4,5]

As survival has improved, strategies for mitigating or preventing the adverse effects of cancer therapy have assumed greater importance. As a result of differences in pediatric hearing assessment protocols,[6,7] variability in hearing outcomes reporting,[3,7,8] and differences in the mechanisms for collecting and reporting audiologic data in multicenter clinical trials,[9,10] it is currently difficult to directly compare or pool ototoxicity data across studies. International standardization in the assessment and reporting of ototoxicity for pediatric

ASSOCIATED CONTENT

Appendix
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patients with cancer would advance patient care and ototoxicity research.

Ototoxicity is typically monitored with serial audiometry, measured for frequencies 0.25 to 8 kHz. Extended high-frequency audiometry (EHF) and otoacoustic emissions (OAEs) are more sensitive measures of ototoxicity.[11-14] EHF audiometry is the measurement of hearing thresholds at frequencies > 8 kHz. It detects ototoxicity earlier because ototoxic damage initially occurs at the base of the cochlea where high frequencies are encoded.[15] OAEs provide an objective evaluation of cochlear outer hair cell function, and changes in OAEs may precede loss of hearing sensitivity.[13,14]

Children's Oncology Group (COG) study ACCL05C1 was designed to inform future ototoxicity studies by identifying the optimal criteria for ototoxicity reporting, to evaluate the feasibility of more sensitive measures of ototoxicity, and to gain pilot experience with a central ototoxicity review mechanism prospectively among pediatric patients who were treated with cisplatin in a cooperative group setting. The specific objectives were to compare contemporaneous ototoxicity scales, evaluate the feasibility of including OAEs and EHF, and assess central review for audiologic results.

PATIENTS AND METHODS

This study was a multi-institutional, multinational COG prospective observational cohort study.

Study Participants

Participants were enrolled between May 2007 and February 2012. Eligibility criteria were 1 to 30 years of age at enrollment, planned treatment with any cisplatin-containing regimen, no prior history of cisplatin therapy, and, for patients enrolled after February 9, 2009, intent to offer enrollment into a companion clinical trial (ACCL0431) for which ACCL05C1 was the mechanism to collect hearing outcomes. ACCL0431 was a randomized trial that evaluated the efficacy of sodium thiosulfate for protection against cisplatin ototoxicity in pediatric patients.[16] ACCL05C1 was approved by the National Cancer Institute's Central Institutional Review Board and by each individual institutional review board at participating institutions. Informed consent or assent was obtained from participants and their guardians, as appropriate, before study entry.

Hearing Evaluation Procedures

A baseline audiologic evaluation was required before the first course of cisplatin, and monitoring evaluations were conducted within 1 week before each subsequent cisplatin course. An end-of-treatment evaluation was completed approximately 4 weeks after the final cisplatin treatment or 4 weeks after hematopoietic cell transplantation for patients who received the procedure.

Audiologic assessments included bilateral measurement of pure tone air conduction thresholds at frequencies of 0.5, 1, 2, 3, 4, 6, and 8 kHz; otoscopy; and middle ear immittance measurement with tympanometry. Audiometric methods included standard audiometry, conditioned play audiometry, or visual reinforcement audiometry, depending on the age and development of the child. Bone-conduction threshold measurement was indicated if air conduction thresholds at 0.5 to 4 kHz were > 20 dB hearing level (HL) or if otoscopy or tympanometry revealed conductive middle ear pathology. When audiometry was unreliable or unobtainable because of age or health status, the protocol recommended estimation of hearing thresholds with frequency-specific evoked auditory brainstem potentials, auditory brainstem response (ABR), or auditory steady state response (ASSR) at frequencies of 0.5 to 4 kHz and 8 kHz, if possible, when this testing was feasible and available.

To evaluate the feasibility of OAEs and EHF, institutions were asked to include these measures with each audiologic evaluation, if available. Distortion product evoked otoacoustic emissions (DPOAEs) or transient evoked otoacoustic emissions were obtained when middle ear function was normal, and EHF thresholds were requested for participants ≥ 5 years of age.[17]

Ototoxicity Classification Systems Evaluated

Four ototoxicity systems were evaluated, the American Speech-Language-Hearing Association Ototoxicity Criteria (ASHA),[18] Common Terminology Criteria for Adverse Events (CTCAE) version 3.0,[19] the Brock Criteria (Brock),[20] and the International Society of Pediatric Oncology Ototoxicity Scale (SIOP).[7] Specific definitions are listed in Appendix Table A1 (online only).

ASHA[18] is a binary criterion (yes or no) that is designed for early ototoxicity detection. Ototoxicity is defined as a ≥ 20-dB decrease in pure tone threshold at one test frequency or a ≥ 10-dB decrease in pure tone threshold at two adjacent test frequencies. ASHA ototoxic change criteria exceeds test-retest variability and indicates a loss of hearing as a result of ototoxicity.

CTCAE[19] grading is the standard approach for toxicity reporting in National Cancer Institute clinical trials. Ototoxicity is graded on an ordinal scale from 1 to 4, with 4 being the most severe. Grades 1 and 2 are based on change in hearing thresholds from baseline, and grades 3 and 4 relate to recommendations for hearing intervention. CTCAE version 3.0 was the current version at the time of study activation.

Brock[20] was developed to compare hearing outcomes at the end of treatment in international clinical trials; a statistically significant relationship has been established between cumulative cisplatin dose and Brock grade.[18] Ototoxicity is graded on an ordinal scale of 1 to 4, where 4 is the most severe. Grades are based on hearing threshold levels ≥ 40 dB HL, rather than a change in threshold compared with baseline.

SIOP[7] was also developed to report hearing outcomes in international clinical trials for pediatric patients who were treated with platinum chemotherapy. Grading is based on hearing thresholds > 20 dB HL by using an ordinal scale of 1 to 4, where 4 is the most severe.

Procedures for Ototoxicity Determination

For each hearing evaluation, ototoxicity determination and grading was conducted by the testing audiologist and two central study audiologists (BB, KK). Raw audiologic data, including audiograms, tympanograms, OAE printouts, ABR waveforms, and the evaluation report, were faxed from the institutions to the COG Data Center and were then distributed to the study audiologists for independent central review. If the records indicated that specific tests were completed but the raw data were not submitted, missing data were requested from the institution. Central reviewers were blinded to the institutional audiologist's assessment and to each other's assessments. Any initial discrepancies between the two central reviews were discussed and resolved to achieve consensus. Because SIOP was added after completion of the study—as it was not available at the time of study development—it was only evaluated by one central reviewer (K.K.).

Audiograms were reviewed to determine if ototoxicity occurred according to ASHA and were graded for severity of hearing loss according to CTCAE, Brock, and SIOP. If middle ear pathology or conductive hearing loss was present, ototoxicity determination was based on bone conduction thresholds, and if bone conduction thresholds were not obtained, then the assessment was categorized as not evaluable. Ototoxicity for EHF was determined by using ASHA. When ABRs or ASSRs were measured, results were classified as normal or abnormal by the testing audiologist. If the ABR or ASSR was categorized as abnormal, ototoxic change in ABR and ASSR thresholds—relative to a previous ABR or ASSR—was determined according to ASHA. ABR and ASSR results and behavioral audiometric thresholds were not directly compared, and ototoxicity grading was not

applied to ABR and ASSR results. OAEs were classified as abnormal if a loss of OAEs occurred at any frequency within the 2- to 8-kHz range when middle ear function was normal.

Comparison of Ototoxicity Systems

Two approaches were used to compare the four different ototoxicity systems. First, within each patient, the earliest date of detection of ototoxicity was determined for each of the four measures (ASHA, CTCAE, Brock, and SIOP). These dates were ranked, with rank 1 for the earliest and rank 4 the latest. If more than one ototoxicity measure was met at the same time point, both were given a score that represented the mean of the corresponding ranks. For example, if three scales were second in detecting ototoxicity, each received a score of 3, which was the average of ranks 2 to 4. If none of the measures met ototoxicity criteria at any time point on study, the date was arbitrarily set as September 30, 2015, later than any study evaluation date. Rank scores among all patients were summarized for each measure; thus, a lower rank score indicates earlier detection of ototoxicity by that measure. Because not every audiogram was evaluable by all four scales, the rank score reflected a combination of sensitivity and feasibility.

Second, we reviewed false-positive rates for each ototoxicity system. A false positive was defined as identification of ototoxicity at one time point and normal hearing or no ototoxicity on a subsequent evaluation. If more than one false positive occurred in the same patient, each instance was counted. The last hearing assessment could never be designated a false positive as there would be no later assessment to confirm or change the assignment of ototoxicity.

Statistical Analysis

Descriptive statistics summarized patient characteristics, the number of evaluable assessments, and the prevalence of ototoxicity and severe ototoxicity (grades 3 or 4) by the different ototoxicity measures at the end of therapy and among all time points. McNemar's test was used to compare the frequency of ototoxicity or severe ototoxicity by two different measures at the end of therapy. Two-sided nonparametric binomial sign test was used to compare rank scores for initial detection of ototoxicity between two measures; the scale with the lowest average rank was used as reference and compared with each of the other three scales. Bonferroni adjustment for the six possible pairwise comparisons would require a comparison between two scales to have a P value of $< .0083$ to be considered statistically significant. Initial agreement between the two central reviewers and between the institutional review and consensus central review was examined by using the simple Kappa statistic for comparisons between two categories and the weighted Kappa when data included more than two categories. Any ototoxicity, ototoxicity grade (1 to 4), and ototoxicity severity (severe v none or mild) were compared.

Strength of agreement was defined as slight (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.00).[21] All analyses were performed by using SAS (SAS/STAT User's Guide, Version 9.3; SAS Institute, Cary, NC).

RESULTS

During the study period, 301 participants from 53 institutions enrolled, of whom 131 coenrolled in ACCL0431. There were 17 participants who were ineligible (prior receipt cisplatin [n = 1], enrolled after February 9, 2009, and not eligible for ACCL0431 [n = 16]), which left 284 eligible participants. Table 1 lists the demographic characteristics of the cohort. Median age was 10.2 years (range, 0.1 to 21.3 years) and the median cumulative dose of cisplatin was 395 mg/m^2 (range, 48 to 623 mg/m^2). There were 27 patients who underwent hematopoietic stem cell transplantation.

Table 1. Patient Characteristics of the Study Cohort (N = 284)

Characteristic	Value
Age, median (range), years	10.2 (0.1-21.3)
Male, No. (%)	168 (59)
Diagnosis, No. (%)	
Germ cell tumor	51 (18)
Hepatoblastoma	13 (5)
Medulloblastoma or supratentorial primitive neuroectodermal tumor	63 (22)
Neuroblastoma	53 (19)
Osteosarcoma	84 (30)
Other	20 (7)
Prior therapy before enrollment,* No. (%)	87 (31)
Chemotherapy multiagent systemic	32 (11)
Chemotherapy single agent systemic	21 (7)
Cranial radiation	42 (15)
Cumulative dose cisplatin, median (range), mg/m^2	395 (48-623)
Hematopoietic stem cell transplantation, No. (%)	27 of 282 (10)

*Missing in one patient.

A total of 1,436 audiologic evaluations were reviewed. Hearing assessment methods and the number of evaluations that included OAEs and EHF are listed in Table 2. Central review for ototoxicity was not possible for 54 evaluations (4%) as a result of missing test data.

Table 3 lists the prevalence of ototoxicity and severe ototoxicity at the end of treatment by the four ototoxicity systems. A discordant pair occurred in the comparison of two systems when ototoxicity was classified by one system and not the other. Compared with CTCAE, SIOP detected significantly more ototoxicity (11 v 1 discordant pairs; $P = .004$), whereas Brock criteria detected significantly fewer patients with any ototoxicity (0 v 19 discordant pairs) or severe ototoxicity (0 v 22 discordant pairs; $P < .001$ for both). In 19 patients who had ABR or ASSR at the end of treatment, ototoxicity occurred in eight and could not be determined in two patients due to lack of a prior comparison. Ototoxicity in EHF thresholds occurred in 69 (68%) of 101 patients and 25 patients (25%) had ototoxicity in EHF range but not in the conventional frequencies. DPOAEs were categorized as abnormal in 120 (60%) of 201 patients at the end of therapy.

Table 2. Hearing Assessment Methods

Type of Hearing Assessment Completed	Evaluation (N = 1,436)
Audiometry	1,279 (89)
Earphones or headphones	1,174 (92)
Sound field	89 (7)
Earphones or headphones and sound field	16 (1)
ABR/ASSR	102 (7)
OAEs only, without audiometry or ABR/ASSR	55 (4)
Evaluations that included DPOAEs	1,208 (84)
Evaluations that included TEOAEs	192 (13)
Evaluations that included EHF	609 (42)
EHF measured at baseline in patients age ≥ 5 years	107 of 191 (56)

NOTE. Data are given as No. (%).
Abbreviations: ABR, auditory brainstem response; ASSR, auditory steady state response; DPOAE, distortion product evoked otoacoustic emission; EHF, extended high-frequency audiometry; TEOAE, transient evoked otoacoustic emission.

Table 3. Incidence of Any Grade Ototoxicity and Severe Ototoxicity at the End of Treatment by Grading Criteria by Central Review

Variable	ASHA	CTCAE*	Brock	SIOP
No. evaluable for ototoxicity by specified criterion (from 222 total)	209	215	210	215
Any ototoxicity at end of therapy†	117 (56%); $P = .0002$	109 (51%); Ref	85 (40%); $P < .001$	118 (55%); $P = .004$
4 weeks postcisplatin only	100 of 186 (54%)	90 of 189 (48%)	69 of 185 (37%)	97 of 189 (51%)
4 weeks post-transplantation only	17 of 23 (74%)	19 of 26 (73%)	16 of 25 (64%)	21 of 26 (81%)
Severe ototoxicity (grades 3 to 4) at end of therapy†		37 of 209 (18%); Ref	14 of 210 (7%); $P < .001$	47 of 215 (22%); $P = .02$
4 weeks postcisplatin only		25 of 185 (14%)	8 of 185 (4%)	34 of 189 (18%)
4 weeks post-transplantation only		12 of 24 (50%)	6 of 25 (24%)	13 of 26 (50%)

NOTE. *P* values derived by using McNemar's test compared with CTCAE are used as the reference (Ref) and are based on patients with both criteria available.
Abbreviations: ASHA, American Speech-Language-Hearing Association Ototoxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; SIOP, International Society of Pediatric Oncology.
*Six patients with grade not specified were excluded from the computation of severe ototoxicity using CTCAE.
†End of therapy means after the last dose of cisplatin or hematopoietic stem cell transplantation.

Table 4 lists the number of assessments that indicated ototoxicity for all audiometric evaluations combined. The number of evaluable audiograms was comparable between CTCAE, Brock, and SIOP, with slightly fewer by ASHA. Fewer patients had at least one audiogram that was evaluable by ASHA compared with the other scales. When evaluating time to detection of ototoxicity, on average, SIOP detected ototoxicity the earliest with the lowest mean rank score of 2.24, followed by ASHA, CTCAE, and Brock. Brock never detected ototoxicity before SIOP, ASHA, or CTCAE. Table 4 also illustrates that false positives were highest for ASHA and SIOP and lowest for Brock.

Agreement in the designation of ototoxicity and ototoxicity grade for all evaluations is shown in Table 5. Agreement between the two central reviewers was almost perfect. Agreement between the consensus central review and institutional audiologist was almost perfect for ASHA and Brock but was worst for CTCAE.

DISCUSSION

In this prospective, multi-institutional, multinational clinical trial among a large cohort of cisplatin-treated children and adolescents, variability of ototoxicity (40% to 56%) and severe ototoxicity (7% to 22%) reported by the different approaches was substantial. The current lack of an international standard for ototoxicity reporting prevents comparison of results within and across diseases and studies.

We found that SIOP might be the optimal criteria on the basis of the high number of evaluable assessments, sensitivity, and earliest time to detection of ototoxicity. ASHA had the lowest number of evaluable assessments, as it requires comparison with baseline and does not use a severity grading scale. Brock had the lowest false-positive rate and the highest inter-rater agreement; however, the scale identified ototoxicity in fewer patients, at a later time in treatment, and reported significantly fewer patients as having any ototoxicity and severe ototoxicity. Because Brock does not capture ototoxicity until hearing thresholds are $\leq$ 40 dB HL, it does not detect mild hearing loss that is communicatively and educationally important for developing children and adolescents.[22,23] CTCAE was not the optimal measure by any evaluation and had the worst agreement between local and central audiologists.

In previous pediatric multicenter clinical studies, approximately 30% of hearing assessments were not evaluable for ototoxicity as a result of incomplete or missing test results or lack of a frequency-specific measurement.[3,9,10] In contrast, only 4% of audiologic evaluations were missing data for central review and 3% of end-of-treatment audiograms were not evaluable for ototoxicity in this study. Our favorable results may have occurred because central review was completed soon after audiology results were submitted by the institution to COG and any missing test data were requested in real time. In addition, as the testing audiologist was asked to grade the results, he or she was aware of the information needed for ototoxicity grading.

Table 4. Comparison of Different Ototoxicity Criteria by Central Review

Variable	ASHA	CTCAE	Brock	SIOP
No. of evaluable audiograms	969 of 1,042* (93%)	1,223 of 1,279 (96%)	1,228 of 1,279 (96%)	1,244 of 1,279 (97%)
Detection of ototoxicity, all evaluations	410 of 969 (42%)	367 of 1,223 (30%)	260 of 1,228 (21%)	429 of 1,244 (34%)
No. of patients with at least one follow-up evaluable audiogram	245	261	260	262
Detection of ototoxicity, all patients	139 of 282† (49%)	129 of 282 (46%)	100 of 282 (35%)	144 of 282 (51%)
Initial detection of ototoxicity, mean rank (range)	2.34 (1-4)	2.51 (1-4)	2.91 (1.5-4)	2.24 (1-3.5)
Initial detection rank comparison, *P*‡	.06	< .001	< .001	—
False positives (evaluations) identified§	21	13	6	19

Abbreviations: ASHA, American Speech-Language-Hearing Association Ototoxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; SIOP, International Society of Pediatric Oncology.
*Does not include baseline evaluations.
†Ototoxicity could not be determined in two patients.
‡Initial detection rank score between SIOP and the other criteria were compared by (binomial) sign test.
§False positive was defined as the indication of ototoxicity at one time point but no ototoxicity in a latter study.

Table 5. Agreement Between Central Reviewers and Between Central and Institutional Reviewers*

Variable	ASHA		CTCAE		Brock	
	Kappa	95% CI	Kappa	95% CI	Kappa	95% CI
Agreement between two central reviewers						
Ototoxicity incidence (yes *v* no)	0.92	0.89 to 0.95	0.92	0.90 to 0.95	0.98	0.97 to 1.0
Ototoxicity grade (1 to 4)	NA	NA	0.90	0.88 to 0.92	0.98	0.97 to 0.99
Ototoxicity severity (severe *v* none or mild)	NA	NA	0.80	0.74 to 0.87	0.93	0.86 to 1.0
Agreement between central and institutional reviewer						
Ototoxicity incidence (yes *v* no)	0.84	0.80 to 0.87	0.87	0.84 to 0.90	0.91	0.88 to 0.94
Ototoxicity grade (1 to 4)	NA	NA	0.84	0.81 to 0.86	0.89	0.86 to 0.92
Ototoxicity severity (severe *v* none or mild)	NA	NA	0.69	0.60 to 0.78	0.85	0.75 to 0.95

NOTE. Simple Kappa statistic was used for comparisons between two categories and weighted Kappa was used when data included more than two categories.
Abbreviations: ASHA, American Speech-Language-Hearing Association Ototoxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable.

There have been concerns about the reliability of institutional ototoxicity reporting. In a study of 120 children who were treated for hepatoblastoma, prevalence of CTCAE grade 3 and 4 ototoxicity was 4% by institutional reporting compared with 38% by central auditory specialist review.[9] Having institutional audiologists review and report ototoxicity may have overcome these challenges as there was substantial to almost perfect agreement between institutional review and central review in our study. However, in light of its feasibility in the cooperative group setting demonstrated here, we believe central audiology review should be used in future clinical trials in which ototoxicity is a primary end point because it ensures consistency in the analysis of outcomes. This is important in the pediatric setting when test results may be incomplete or confounded by conductive middle ear pathology. In addition, collection of raw audiology data allows rescoring of ototoxicity by alternate approaches that might be developed in the future, as occurred in our study with SIOP.

OAEs were included in 84% of evaluations and are likely feasible for ototoxicity monitoring in future COG clinical trials; however, OAEs cannot estimate hearing thresholds, and, at this time, there are no accepted criteria for ototoxic change or grading of OAEs. Consistent with other studies, EHF was more sensitive to ototoxicity than was conventional audiometry[12,24]; however, it may not be feasible to implement in COG group-wide trials as it was only obtained in 56% of participants who were $\geq$ 5 years of age. The most common reason cited by institutional audiologists for not including EHF was lack of EHF instrumentation.

ASHA and SIOP had the highest rates of false positives, as defined by this study. Although we considered reversals in ototoxicity designation as false positives, it is possible that these changes could reflect a process of fluctuation in hearing levels with recovery during ototoxic treatment. Truong et al[25] reported fluctuating tinnitus and hearing loss with accompanying changes in DPOAEs in a patient age 16 years during cisplatin chemotherapy. They hypothesized that in some dosing regimens, early acute ototoxicity may damage strial cells and supporting cells within the cochlea that have the potential to recover, whereas damage to outer hair cells results in permanent hearing loss.

The strengths of our report are the large number and diversity of children and adolescents included and the number of participating institutions, which improve the generalizability of our findings. Other strengths are the use of two independent central audiology reviewers as well as novel approaches to compare ototoxicity systems; however, our results must be interpreted in light of the limitations of the study. First, because SIOP was developed after initiation of this trial, inter-rater reliability of this approach could not be evaluated, although given the excellent agreement in ototoxicity designations between the two central reviewers, we do not anticipate that this absence would have affected our conclusions. Second, as there is not a gold standard measure of ototoxicity, one cannot calculate specificity or sensitivity. Third, another recently developed ototoxicity criteria, the Chang Criteria,[6] was not evaluated in this study.

In conclusion, SIOP may be superior to ASHA, Brock, and CTCAE scales for classifying ototoxicity in pediatric patients who are treated with cisplatin. Future studies should evaluate inter-rater reliability of the SIOP scale.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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Appendix

Table A1. Ototoxicity Criteria Definitions

Scale	Determination of Ototoxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ASHA (ASHA 1994)	Change in hearing threshold compared with baseline	Does not use numeric grades to distinguish severity of ototoxicity; ototoxicity is indicated by ≥ 20 dB threshold shift at one frequency, > 10 dB shift at two adjacent frequencies, or loss of response at three consecutive frequencies where responses were obtained at baseline				
NCI CTCAE v3	Change in hearing compared with baseline	Normal hearing, no change in hearing from baseline	Threshold shift or loss 15-25 dB compared with baseline, averaged at two or more contiguous frequencies in at least one ear	Threshold shift of loss 25-90 dB, averaged at two or more contiguous frequencies in at least one ear	Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (> 20 dB bilateral HL speech frequencies; > 30 dB unilateral HL); and requiring additional speech-language–related services	Indication for cochlear implant and requiring additional speech-language– related services
Brock (Brock 1991)	Bilateral threshold HL	Hearing threshold < 40 dB at 1-8 kHz	≤ 40 dB at 8 kHz	≤ 40 dB at ≥ 4 kHz	≤ 40 dB at ≥ 2 kHz	≤ 40 dB at ≥ 1 kHz
SIOP ototoxicity scale (Brock 2012)	Threshold HL	Hearing thresholds ≥ 20 dB at 1-8 kHz	> 20 dB HL above 4 kHz	> 20 dB HL at ≥ 4 kHz	> 20 dB HL at ≥ 2-3 kHz	> 40 dB HL at ≥ 2 kHz

Abbreviations: ASHA, American Speech-Language-Hearing Association Ototoxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; HL, hearing level; NCI, National Cancer Institute; SIOP, International Society of Pediatric Oncology.